Patients' perspectives. Subjective experiences and attitudes of patients with recent onset schizophrenia

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Chapter 3.3.

Subjective experience and striatal dopamine D$_2$ receptor occupancy in patients with schizophrenia stabilized on olanzapine or risperidone


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Summary

**Objective:** The authors’ goal was to study the relationship between subjective experience during treatment with olanzapine or risperidone and dopamine D₂ receptor occupancy in stabilized patients with schizophrenia.

**Method:** Subjective experience, psychopathology and extrapyramidal symptoms were assessed and D₂ receptor occupancy was determined with $[^{123}\text{I}]$IBZM SPECT in 22 patients whose schizophrenia was stabilized by olanzapine or risperidone.

**Results:** Subjective experience, depression, and negative symptoms were related to D₂ receptor occupancy, but extrapyramidal symptoms were not.

**Conclusions:** These results provide preliminary evidence that negative subjective experience is related to high D₂ receptor occupancy. Longitudinal study is required because this relationship may have implications for dosing strategies.
3.3.1. Introduction

The subjective experience of patients treated with antipsychotic medication is related to quality of life (1) and predicts medication compliance (1-3). Subjectively experienced side effects are more distressing than other side effects (4).

Occupancy of dopamine D₂ receptors in the striatum by antipsychotic medication is thought to influence patients' subjective experiences. The influence of cocaine on the dopamine system has a profound effect on subjective experience (5). The striatum is involved in the control of motivation and reward. Extrapyramidal symptoms are related to D₂ receptor occupancy (6) and, in particular, akathisia has an important subjective component.

Olanzapine and risperidone may be associated with a better subjective experience than typical antipsychotic drugs (7, 8). However, if the severity of negative subjective experience is related to D₂ receptor occupancy of olanzapine or risperidone, then these agents might not demonstrate more benefits for subjective experience than typical antipsychotic drugs in doses that lead to the same range of D₂ receptor occupancy (9).

In this study, we evaluated the relationship between subjective experience and striatal D₂ receptor occupancy in patients whose schizophrenia was stabilized by olanzapine or risperidone.

3.3.2. Method

Twenty-one patients with schizophrenia and one patient with schizoaffective disorder, diagnosed according to the DSM-IV criteria were included in this study. Four of the patients were female and 18 were male; their mean age was 22 years (SD =4, range =16-28). Exclusion criteria were neurological or endocrine disease and mental retardation. Nine healthy comparison subjects were also included; their mean age was 24. After a complete description of the study to the subjects, written informed consent was obtained from all.

Patients' subjective experience during the previous 7 days was measured with the Subjective Well-being under Neuroleptic treatment scale (1) and the Subjective Deficit Syndrome Scale (10).

Patients' psychopathology was assessed with the Positive and Negative Syndrome Scale and the Montgomery-Åsberg Depression Rating Scale. Extrapyramidal symptoms and akathisia were assessed with the Simpson Angus Rating Scale (range=0-40) and the Barnes Rating Scale for Drug-Induced Akathisia, respectively.

Single photon emission computed tomography imaging (SPECT) was performed with a brain-dedicated SPECT camera 2 hours after intravenous injection of 110 MBq of iodobenzamide ([¹²³I]IBZM). Specifications and
imaging procedures have been described elsewhere (12). SPECT imaging was performed after a stable dose period of at least 6 weeks of olanzapine (n=15, mean dose=14.7 mg, SD=5.8, range=5-30) or risperidone (n=7, mean dose=4.1 mg, SD=0.9, range=3-6). Subjective experience, psychopathology, and extrapyramidal symptoms were assessed within 2 days after SPECT imaging. None of the patients used alcohol, cannabis, or other nonprescribed drugs. Patients were blind to the main goal of this study, i.e., assessment of the relationship between medication and subjective experience.

Semiquantification of $[^{123}\text{I}]$IBZM binding was performed by placing a template of fixed regions of interest over the striatum and occipital cortex (12). Specific striatal binding was defined as striatal binding divided by occipital binding (12). All analyses were performed blind to clinical data. The nine healthy comparison subjects had a mean $[^{123}\text{I}]$IBZM binding ratio of 1.92 (SD 0.08), which was used to calculate the percentage of occupancy by medication as (ratio striatum/occipital region)-1/(1.92-1)*(-100)+100 (12).

We conducted one-tailed analyses because we hypothesized that high D$_2$ receptor occupancy was related to worse subjective experience. Analyses were performed for the total group of patients (n=22) and for the group receiving olanzapine (n=15). Analyses for the subgroup using risperidone were not performed, because there was minimal variation of doses in this group.

### 3.3.3. Results

Both self-control and emotional regulation items on the Subjective Well-being under Neuroleptic treatment scale correlated with the percentage of D$_2$ receptor occupancy (Table 1). Positive and Negative Syndrome Scale negative symptoms ratings and the Montgomery-Asberg Depression Rating Scale scores also correlated with D$_2$ receptor occupancy (Table 1). Other Positive and Negative Syndrome Scale subscale ratings were not significantly correlated with D$_2$ receptor occupancy.

Simpson-Angus ratings were zero in most patients, but two patients each had a total score of 3 and two patients each had a total score of 4. Six patients had a score of 2 on the Barnes scale. Extrapyramidal symptoms were not correlated with percentage of D$_2$ receptor occupancy.
Table 1. Correlations between D₂ Receptor Occupancy and Subjective Experience and Psychopathology in 22 patients with schizophrenia stabilized by olanzapine or risperidone

<table>
<thead>
<tr>
<th>Measure of Subjective experience or psychopathology</th>
<th>Spearman correlation of score with percentage of D₂ receptor occupancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjective Well-being under Neuroleptic treatment scale</td>
<td>rₛ p</td>
</tr>
<tr>
<td>Total</td>
<td>-0.33 0.06</td>
</tr>
<tr>
<td>Emotional regulation</td>
<td>-0.36 0.06</td>
</tr>
<tr>
<td>Self-control</td>
<td>-0.41 0.03</td>
</tr>
<tr>
<td>Subjective Deficit Syndrome Scale total</td>
<td>0.30 0.09</td>
</tr>
<tr>
<td>Montgomery-Asberg Depression Rating Scale</td>
<td>0.46 0.02</td>
</tr>
<tr>
<td>Positive and Negative Syndrome Scale</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>0.45 0.02</td>
</tr>
<tr>
<td>Positive</td>
<td>0.26 0.12</td>
</tr>
<tr>
<td>General</td>
<td>0.22 0.16</td>
</tr>
</tbody>
</table>

In the subgroup of patients using olanzapine, a significant correlation was found between D₂ receptor occupancy percentages and the Subjective Well-being under Neuroleptic treatment scale self-control score (rₛ=-0.53, n=15, p=0.02) and the Subjective Deficit Syndrome Scale total score (rₛ=0.45, n=15, p=0.05). Olanzapine dose correlated with D₂ receptor occupancy (rₛ=0.60, n=15, p=0.01).

The average D₂ receptor occupancy was 67% in the olanzapine group and 77% in the risperidone group. The correlations found would not have reached statistical significance if they had been corrected for multiple comparisons by the Bonferroni test.

3.3.4. Discussion

We found a correlation between striatal D₂ receptor occupancy by olanzapine and risperidone and subjective experience, negative symptoms, and depression, in the absence of extrapyramidal symptoms. Higher doses of olanzapine were correlated with higher D₂ receptor occupancy and worse subjective experience. Negative subjective experience might be more sensitive to D₂ receptor occupancy than extrapyramidal symptoms. The substantial D₂ receptor occupancy of olanzapine and risperidone we found is in agreement with recent findings of others (9).

Our study design permitted assessment only of correlations between subjective experience and D₂ receptor occupancy. Therefore, a longitudinal study is required to confirm these results, since a relationship between higher D₂
receptor occupancy and worse subjective experience may have important implications for dosing strategies and compliance with antipsychotic medication.
References


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